



Multimodal Models Using Circulating Extracellular Vesicles And Imaging Biomarkers Improve Detection Of Mild Cognitive Impairment

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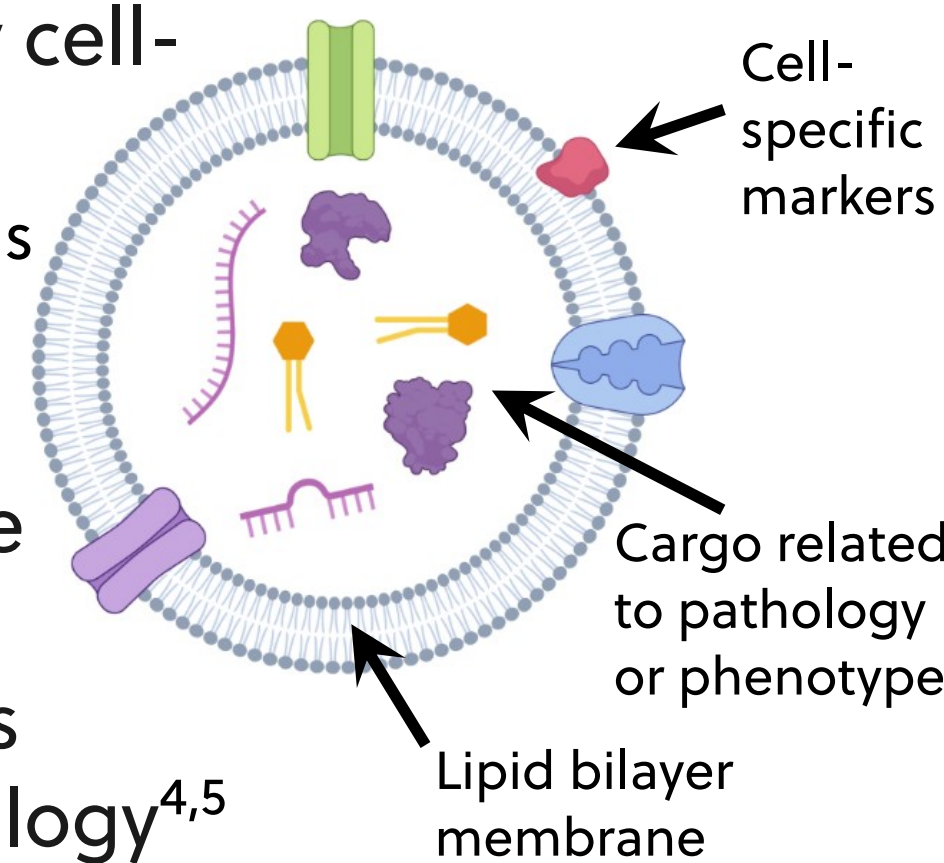
BACKGROUND

■ Early detection of mild cognitive impairment (MCI) is critical for prevention and intervention of dementia

■ Extracellular vesicles (EVs) carry cell-specific markers and cargo¹⁻³

- More specificity than plasma proteins
- Circulating EVs capture cellular changes upstream of disease

■ In contrast, magnetic resonance imaging (MRI) captures the neuroanatomical consequences consequences of disease pathology^{4,5}



OBJECTIVES

Combining EV and MRI metrics as complementary biomarkers could improve early detection of MCI.

- (1) Measure cell-specific EV metrics in MCI
- (2) Measure structural and vascular MRI metrics in MCI and correlate them with EV metrics
- (3) Integrate EV and MRI metrics to distinguish MCI

METHODOLOGY

Nested cohort selection

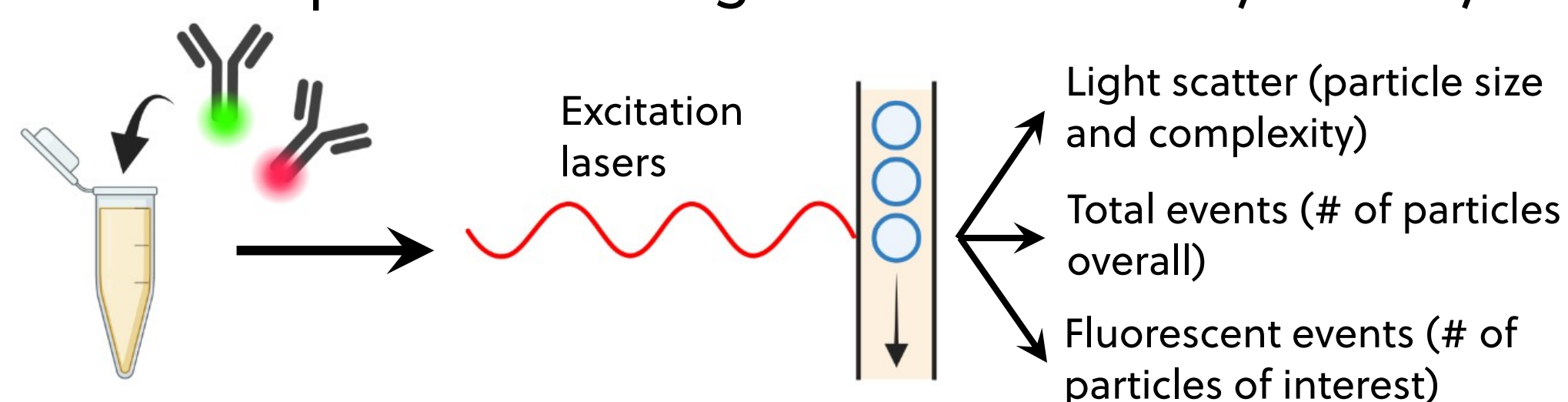
A nested cohort of 68 participants were selected from the Gait & Brain Study⁶. Criteria included:

- Diagnosed with normal cognition (NC, n=35) or MCI (n=33)
- Blood draws and MRI collected at time of recruitment
- No other disease with neurological symptoms or psychiatric disease

Quantification of plasma EVs

Platelet-poor participant plasma was incubated with fluorescent antibodies targeting markers of interest:

- L1 cell adhesion molecule (L1CAM): Neuron-specific marker
 - Transmembrane protein 119 (TMEM119): Microglia-specific marker
 - Beta amyloid 42 (Aβ42): Protein in Alzheimer's Disease progression
 - Phospho-tau at threonine 181 (pTau181): Pathological tau isoform
 - Neurofilament light chain (NfL): Structural protein in axons
- EVs were quantified using nanoscale flow cytometry.



Quantification of MRI metrics

Participant MRI were analyzed using a semiautomated pipeline⁷ to quantify key features of interest:

- Total intracranial volume (TIV)
- White matter hyperintensities (WMH)
- Gray matter volume (GM vol.)
- Enlarged perivascular spaces (EPVS)
- White matter volume (WM vol.)

RESULTS

Cell-specific pTau181⁺ EVs differ in MCI

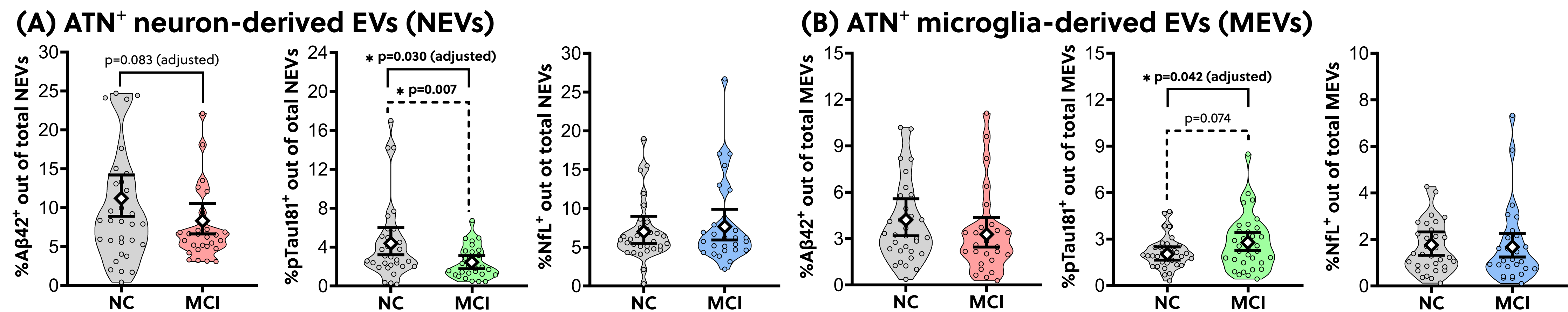


Figure 1. Circulating pTau181⁺ NEVs/MEVs are significantly decreased/increased in MCI. Violin plots show the density estimates of the unadjusted ATN⁺ (A) NEV (L1CAM⁺) and (B) MEV (TMEM119⁺) distributions between participants with normal cognition (NC) and MCI, with individual observations shown as jittered points. Diamonds (◇) indicate age and sex-adjusted estimated marginal means ± 95% CI from gamma generalized linear models. * indicates p<0.05 (likelihood ratio test), labelled as before or after covariate adjustments.

Brain atrophy and WMH burden differ in MCI

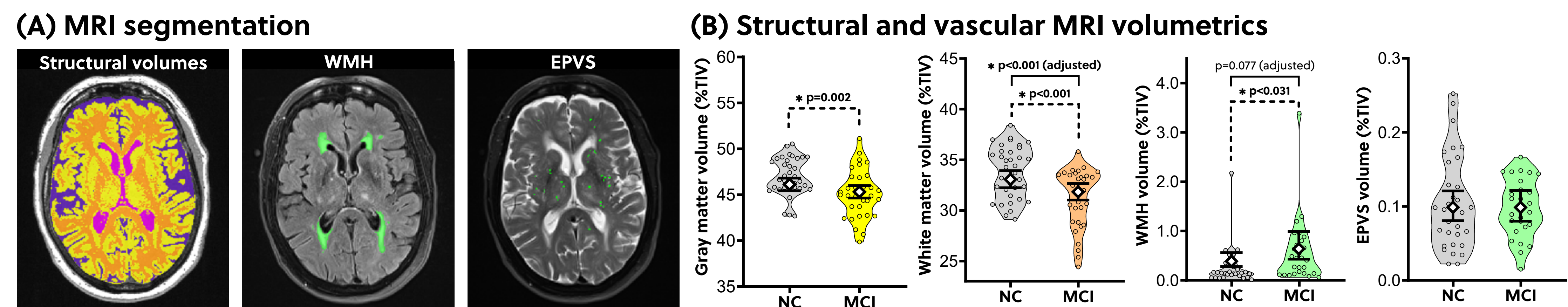
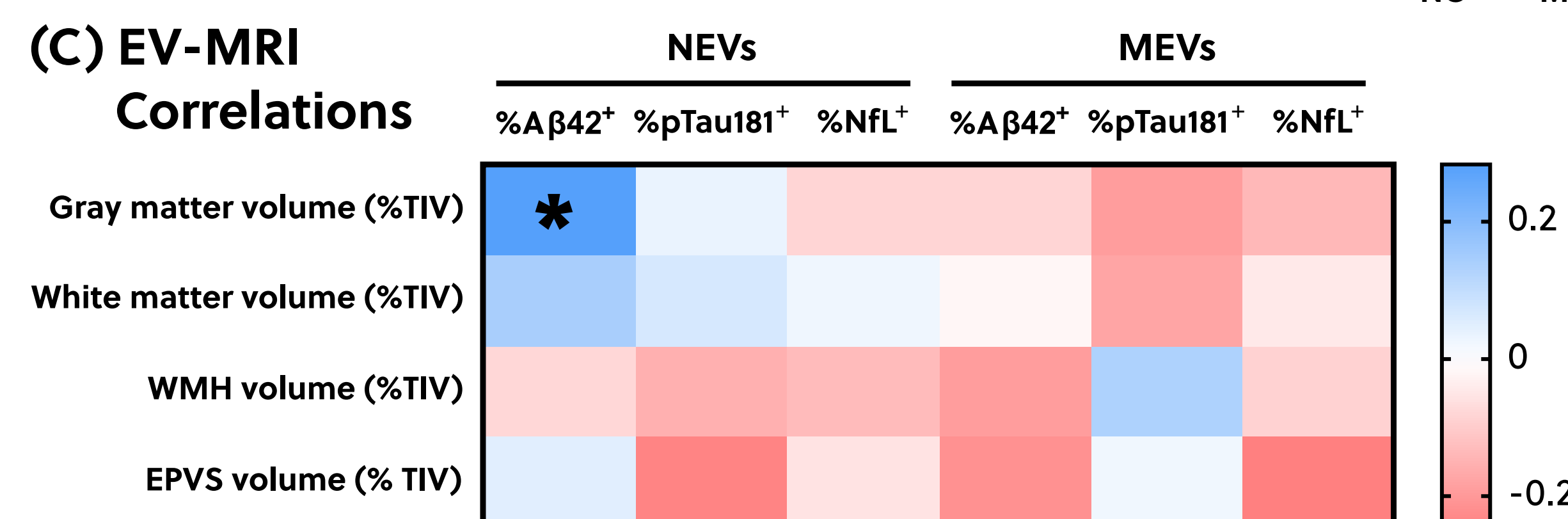


Figure 2. Participants with MCI have increased brain atrophy and WMH burden and %Aβ42⁺ NEVs are positively correlated with gray matter volume. (A) Representative MRI scans showing the tissue, WMH, and EPVS segmentation masks applied to the T1, T2-weighted FLAIR, and T2 sequences. (B) Violin plots show the density estimates of the structural and vascular MRI volumetric distributions between participants with normal cognition (NC) and MCI, with individual observations shown as jittered points. Diamonds (◇) indicate covariate-adjusted estimated marginal means ± 95% CI from gamma generalized linear models, adjusted for age and sex. * indicates p<0.05 (likelihood ratio test), labelled as before or after covariate adjustments. (C) Heatmap showing the Spearman's rank correlations between EV and MRI metrics, adjusted for age and sex. * indicates p<0.05.



Multimodal models distinguish MCI

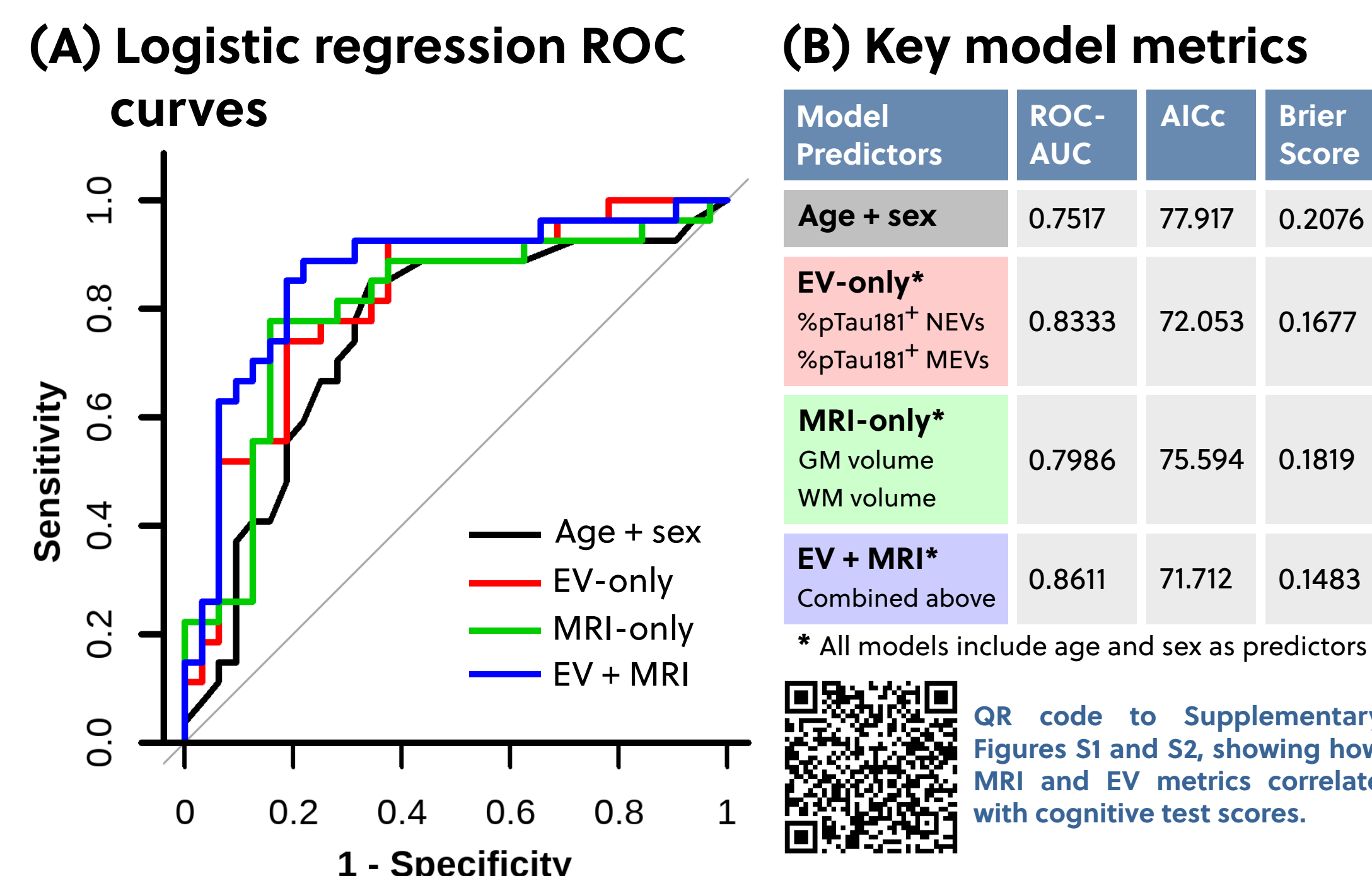


Figure 3. Logistic regression combining EV and MRI metrics better distinguishes MCI. (A) Receiver operating characteristic (ROC) curves for unimodal and multimodal logistic regression models. (B) Table showing area-under-the-curve (AUC), corrected Akaike information criterion (AICc), and Brier score for each model.

CONCLUSIONS

- pTau181⁺ NEVs/MEVs decrease/increase in MCI, suggesting a shift in cell-specific tau dynamics
- WM volume/WMH volume decreases/increases in MCI, supporting previous research
- EV and MRI metrics are mostly uncorrelated, suggesting that they provide complementary rather than similar information as biomarkers
- **Multimodal logistic regression with EV and MRI metrics better identify MCI than unimodal models**

REFERENCES AND ACKNOWLEDGEMENTS

We would like to thank our funding sources for helping provide the resources necessary for this project. Thank you to members of Gait & Brain Lab for assisting with the participant plasma samples and MRI scans and to members of the Vulnerable Brain Lab for their feedback and guidance.

